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Modafinil and cognitive enhancement in schizophrenia & healhy volunteers: the effects of test battery in a randomised controlled trial

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ABSTRACT

Cognitive deficits in schizophrenia have major functional impacts. Modafinil is a cognitive enhancer whose effect in healthy volunteers is well-described, but whose effects on the cognitive deficits of schizophrenia appear to be inconsistent. Two possible reasons for this are that cognitive test batteries vary in their sensitivity, or that the phase of illness may be important, with patients early in their illness responding better. A double-blind, randomised, placebo-controlled single-dose crossover study of modafinil 200mg examined this with two cognitive batteries (MCCB and CANTAB) in 46 participants with under 3 years' duration of DSM-IV schizophrenia, on stable antipsychotic medication. In parallel, the same design was used in 28 age-, sex-, and education-matched healthy volunteers. Uncorrected p values were calculated using mixed effects models. In patients, modafinil significantly improved CANTAB Paired Associate Learning, non-significantly improved efficiency and significantly slowed performance of the CANTAB Stockings of Cambridge spatial planning task. There was no significant effect on any MCCB domain. In healthy volunteers, modafinil significantly increased CANTAB Rapid Visual Processing, Intra-Extra Dimensional Set Shifting and verbal recall accuracy, and MCCB social cognition performance. The only significant differences between groups were in MCCB visual learning. In conclusion, as in earlier chronic schizophrenia studies, modafinil failed to produce changes in cognition in early psychosis as measured by MCCB. CANTAB proved more sensitive to the effects of modafinil in participants with early schizophrenia and in healthy volunteers. This confirms the importance of selecting the appropriate test battery in treatment studies of cognition in schizophrenia.

1. INTRODUCTION

Cognitive impairment, a core feature of schizophrenia, accounts for 20-60% of variance in functional outcome (Green, 1996). From infancy to early adulthood development of many cognitive functions is delayed (Reichenberg et al., 2010), perhaps with deterioration before first episode (Caspi et al., 2003) but then the cognitive function of patients with schizophrenia decline little or no faster than healthy populations until late middle age (Censits et al., 1997, Irani et al., 2012). Milder deficits in clinically unaffected relatives indicate a genetic contribution (Goldberg et al., 1990, Cannon et al., 1994) but the pathophysiological basis of cognitive deficits remain unclear (Harvey et al., 2001). Pharmacological cognition enhancers (CEs), like modafinil, have been used to investigate potential beneficial effects on cognitive domains and also the underlying mechanisms of cognitive deficits.

In healthy volunteers without sleep deprivation, larger studies (n>40) provide moderately consistent evidence of effects of modafinil, though often on the basis of uncorrected significance testing of multiple domains (Turner et al., 2003, Randall et al., 2005, Müller et al., 2013, Mohamed and Lewis, 2014). These include: decreased latency on delayed match to sample, stop signal and Stroop basic recognition tasks, more accurate rapid visual processing, spatial working memory, planning (Stockings of Cambridge task) and pattern recognition memory; but *slower* completion of the Hayling and clock completion tasks. Many such studies have used the Cambridge Neuropsychological Test Automated Battery (CANTAB; www.camcog.com) - a well validated computerised battery which is easily compared to analogous animal task data (Robbins et al., 1994, 1998, Randall et al., 2003, 2004, 2005, Turner et al., 2003, Müller et al., 2013). Modafinil may have a greater effect on scores in samples with lower IQ or greater age, perhaps because these studies avoided ceiling effects (Randall et al., 2005).

A few modafinil trials in schizophrenia have also used CANTAB and modafinil's effects loosely resemble those in healthy volunteers, though studies are often smaller and again rely on uncorrected statistics. Scoriels and colleagues' (2012) single-dose, cross-over comparison of modafinil to placebo in 40 first-episode psychosis patients found significantly improved working memory, spatial working memory accuracy and strategy; fewer discrimination errors in the impulsivity task; and better facial emotion recognition (Scoriels et al., 2011). Turner *et al.*'s (2004) cross-over trial of twenty patients with chronic schizophrenia reported increased latency but more efficient solutions for the Stockings of Cambridge task, and fewer

extradimensional shift (EDS) errors during the set shifting task. Overall these results suggest that modafinil has some beneficial effects on short term memory and attention, as well as on planning and set shifting in schizophrenia, although the mechanism of action is disputed and unclear (Gerrard and Malcolm, 2007, Battleday and Brem, 2015). This is arguably consistent with imaging studies which show increased anterior cingulate and dorsolateral prefrontal activation during cognitive and motor control tasks (Spence et al., 2005, Hunter et al., 2006). Conversely, small, less powerful parallel-arm studies found no effects of modafinil on cognition (Sevy et al., 2005, Pierre et al., 2007).

Only one trial has evaluated modafinil in schizophrenia using the MATRICS Consensus Cognitive Battery (MCCB) (Michalopoulou et al., 2015). The MCCB has the advantages that it is accepted as a viable endpoint measure for clinical trials by the FDA, was developed specifically for use in schizophrenia, and has extensive normative data. Unlike CANTAB, MCCB's administration is heavily language based, and it is not derived from equivalent animal data (Kern et al., 2008, Nuechterlein et al., 2008). In this trial, Michalopoulou *et al.* (2015) found no significant effect of modafinil on MCCB domain or composite scores or CogState SB (a computer-based battery) in a sample of 48 participants with chronic schizophrenia, mean age 37.2$\pm$9.6 years. Many factors could have contributed to the absence of a measurable effect of modafinil on cognition: (i) modafinil does not enhance cognition in schizophrenia, (ii) modafinil enhances cognition in early schizophrenia but not chronic schizophrenia, or (iii) modafinil enhances cognition but the assessment batteries used are not sufficiently sensitive to detect changes over time.

To distinguish these explanations the current study examined participants in the early stages of schizophrenia with both the CANTAB and MCCB. Our main hypothesis was that compared to placebo, modafinil would have similar effects on cognition in early schizophrenia and healthy volunteers, and hence would normalise deficits in planning strategy, working memory, set shifting and social cognition in early schizophrenia, measured against healthy volunteers' baseline. A secondary hypothesis, that choice of cognitive battery would be an important factor in detecting modafinil-induced change in both patients and healthy volunteers, was tested by comparing CANTAB and MCCB batteries.

2. METHOD

We used a double blind randomised placebo-controlled crossover design to compare the effects of modafinil in participants with early schizophrenia and related disorders, and in matched healthy volunteers. The study in schizophrenia received ethical approval from the Greater Manchester South Research Ethics Committee and the extension to healthy volunteers from Greater Manchester East Research Ethics Committee East (REC numbers 13/NW/0626 and 14/NW/0299).

Participants

Patients aged between 18 and 35 years old were recruited from mental health services of King's Health Partners' (London) and Manchester Academic Health Science Centre. Inclusion criteria were: (i) DSM-IV criteria for schizophrenia, schizophreniform or schizoaffective disorder (confirmed using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998)); (ii) clinically stable in a non-acute phase for at least 8 weeks prior to the screening visit with duration of illness between one month and three years; (iii) treated with stable doses of 2nd generation antipsychotics (excluding clozapine) in the absence of concomitant anticholinergics for a minimum of 4 weeks prior to screening; (iv) a score of <5 on the PANSS conceptual disorganisation, hallucinations, unusual thought content and all negative subscale items; (v) English at a level sufficient to understand and complete study-related procedures, and score ≥ 6 on the Wechsler Test of Adult Reading (Holdnack, 2001). Female participants of child-bearing potential were required to use an acceptable method of contraception for the duration of the study and have a negative pregnancy test result at screening.

Participants were excluded from the study if they met DSM-IV criteria for alcohol or substance abuse (other than nicotine) within the last month or dependence in the last six months preceding the screening visit. They were also excluded if they were being treated with modafinil, agents known to affect cognition (including anticholinergics, clozapine and thioridazine), compounds known to interact with modafinil, or any known drug allergies; a history of significant head trauma, or a serious neurological disorder; an abnormal ECG or physical examination findings; or participation in a study of any psychotropic medication or with a neuropsychological component in the two months preceding the screening visit.

For healthy volunteers (HVs), age and literacy inclusion criteria and all exclusion criteria were identical. HVs were matched to those in the first group on age (± 5 years), gender, ethnicity and years of education.

Procedure

Thirty six HVs and 65 participants with schizophrenia attended visit 1, during which they gave written informed consent, followed by a check of their eligibility. Of these, 28 HVs and 46 schizophrenia patients were confirmed as eligible and included in the double-blind, placebo-controlled, single-dose cross-over study. Two HVs and 6 schizophrenia participants withdrew following randomisation; a further 5 HVs were withdrawn due to an adverse event or because they were unable to complete the study within the timeframe required.

Participants subsequently attended three neuropsychological assessment visits (visits 2-4). They received medication on the day of visits 3 and 4, 2 hours prior to assessment, namely 200mg modafinil on one occasion and an identical placebo tablet at the other visit, in random order. Visits 3 and 4 occurred seven to ten days apart to allow a wash-out period.

Drug Treatment

The dose of 200mg of modafinil was chosen after reviewing pharmacokinetic studies of modafinil and previous studies of modafinil in healthy volunteers (Wong et al., 1999a, 1999b) and in patients with schizophrenia (Turner et al., 2004, Rosenthal and Bryant, 2004, Sevy et al., 2005, Spence et al., 2005, Hunter et al., 2006, Pierre et al., 2007). Participants were told to take the tablet two hours before their appointment and reminded by telephone at the appropriate time, in order that peak plasma levels were reached during assessment, 2-3hrs after oral administration (Wong et al., 1999a, 1999b). Vital signs were recorded at all 4 visits and adverse effects monitored at all visits and by telephone 7-10 days after visit 4.

Allocation

Allocation, carried out via an online system at the King's Clinical Trials Unit, was by minimisation. Smoking status (known to effect cognitive performance) (Lees et al., 2015) and treatment site (to allow for possible differences) were used as stratifying factors. Capsules were supplied in coded bottles containing identical capsules of modafinil and placebo.

Cognitive Tests

Participants completed the MATRICS Consensus Cognitive Battery (MCCB (Kern et al., 2008, Nuechterlein et al., 2008)) and CANTAB Schizophrenia Battery (www.camcog.com). Alternative forms of tests were used at the different visits if they were sensitive to practice effects: these included the MCCB Brief Visuospatial Memory Test-Revised (BVMT-R), Hopkins Verbal Learning Test-Revised (HVLT-R) and Neuropsychological Assessment Battery (NAB) mazes, and the CANTAB Verbal Recognition Memory (VRM), Paired Associates Learning (PAL) and Intra/extradimensional Set Shift (IED).

Statistical Analysis

To test the hypothesis that modafinil in patient participants would increase scores on specific tests towards healthy baselines, we assumed there were no carryover effects due to the wash-out period, but we allowed for period (i.e. time) and sequence effects, whilst our primary effect of interest was the treatment effect (i.e. modafinil versus placebo). We use random effect models with a fixed effect for period and treatment, and a random intercept for each participant. The treatment effect for each outcome was given by a model coefficient, and associated standard error, p-value, and 95% confidence intervals. The effect interpreted was the change in outcome associated with receiving modafinil compared to receiving placebo.

To compare the healthy volunteer and patient samples and test the prediction that modafinil would affect the two groups similarly, we analyse both studies together using the model described above, with the addition of a fixed effect term for study and an interaction between study and drug. The interaction tests whether the treatment effect differs between the samples. The interaction shows the difference in the effect of receiving modafinil compared to placebo, in the healthy volunteers compared to the patient sample.

Across both analyses *p* values were uncorrected for each test, following Rothman (1990). 95% Confidence Intervals (CI) were calculated. Standardized treatment effect sizes were expressed as Glass' δ, final score mean difference between modafinil and placebo divided by the final standard deviation for placebo.

3. RESULTS

Of 28 eligible controls, 21 (75%) completed all test sessions. Of 46 eligible schizophrenia patients, 40 (87%) completed all test sessions. Fourteen (33%) controls and 23 (57.5%)

patients smoked; 15 (71%) controls and 30 (75%) patients were male. Age and full-time education were similar across both groups (Table 1). Verbal IQ as represented by WTAR standardised score differed with effect size -0.81 (Glass' δ, using healthy volunteer SD). Tables S1 and 2 show baseline CANTAB and MCCB scores for the schizophrenia and healthy volunteer groups. Healthy volunteer mean MCCB composite T-scores were 45.2 (SD 10.5), while patients' scores were mean 28.8 (SD 13.0), showing a global deficit of δ-1.26.

There was no significant effect of modafinil on patients' MCCB scores (Figure 1, Tables 2 and S3), though working memory showed a trend towards improvement (1.80, CI -0.09, 3.69; p0.06). Examining patients' CANTAB scores after modafinil (Figure 1, Tables 2 & S4), patients reached solutions for the OTS planning task in non-significantly fewer steps but significantly more slowly (median latency 3.3 seconds more; 95% CI 0.8, 5.8). Modafinil-treatment also resulted in significantly fewer errors on the PAL visual learning task (6 shapes, p0.015).

Healthy volunteers had significantly improved scores after modafinil on the MCCB social cognition domain (5.04, CI 2.23, 7.86, p<0.001), and trends towards better scores for visual learning (2.21; CI -0.39, 4.80; p0.095) and global MCCB (composite score 1.63, CI -0.23, 3.48, p0.085; Figure 1, Tables 3 & S5). They significantly improved on some CANTAB measures of set shifting (IED adjusted errors, p0.008), rapid visual information processing (RVP A, p0.004; and hit probability, p0.001), and verbal recognition memory (VRM immediate free recall novel words, p0.028; Figure 1, Tables 3 and S6).

To examine the prediction that volunteers with and without schizophrenia would respond similarly to modafinil we examined interactions between response to modafinil and group. On the MCCB visual learning healthy volunteers were significantly more responsive to modafinil than patients (4.89; CI 0.07, 9.71; p0.047). There were no other significant differences in MCCB domains or on the CANTAB task scores (Tables 4 & S7), though patients displayed trends towards more slowing of OTS completion after modafinil (-3.66 sec, CI -7.41, 0.08, p0.055) and greater improvement in RVP probability of a hit (0.05, CI -0.01, 0.11, p0.097).

4. DISCUSSION

The primary hypothesis was that modafinil would produce improvements in spatial planning, working memory, set shifting and social cognition, normalising these deficits in early schizophrenia. This hypothesis of specific improvements was not consistently supported in this single-dose crossover study. Though one measure of visual learning (PAL errors on CANTAB) improved, there was no significant effect on other CANTAB or MCCB measures of working memory or planning efficiency (e.g. the One Touch Stockings task or the MCCB problem solving domain). However, patients made choices on the Stockings task significantly more *slowly* after modafinil (i.e. OTS latency increased), an effect previously seen in healthy volunteers (Turner et al., 2003, Randall et al., 2005, Mohamed and Lewis, 2014), with a trend towards a decrease in OTS choices to correct, suggesting a speed/error trade-off, bringing patient's scores closer to those of healthy volunteers at baseline. On the other hand, healthy volunteers improved in their social cognition performance, an effect previously seen in early schizophrenia (Scoriels et al., 2012), while here patients did not.

To test whether HVs and patients responded to modafinil in a similar way, which would suggest that the drug has similar mechanisms in both, an interaction term was added for drug and group (i.e. modafinil and patient) to models of the main effects of group (HV or patient) and drug (baseline, placebo or modafinil) with appropriate adjustment for session (baseline, first or second follow-up) on the various neurocognitive measures. Confidence intervals were wide, given the limited numbers and we found only one significant difference in modafinil's effect on schizophrenia and HV groups: a significant difference in MCCB visual learning, where healthy volunteers but not patients improved (Table 4). Admittedly, the positive finding could just be an artefact of multiple hypothesis testing. Alternatively, the MCCB domain score could be more sensitive to rapid processing than the CANTAB's PAL task, since like the MCCB domain score some CANTAB rapid visual processing (RVP) measures improved in HV but not patients. The results are consistent with those of previous studies investigating the effects of modafinil, including improved performance on the same visual processing measures in healthy volunteers (Randall et al., 2005), an effect not demonstrated in schizophrenia sufferers (Scoriels et al., 2012), and an improvement in the OTS spatial planning task (Turner et al., 2003, Turner et al., 2004, Müller et al., 2013).

Healthy volunteers also differed from patients in that modafinil improved their social cognition task performance. Between the two batteries this is tested by one task, the

MSCEIT, with several elements (Kern et al., 2008, Nuechterlein et al., 2008). The complexity of the MSCEIT, which like many social cognitive tasks has appreciable demands on working memory and other executive functions, makes this difficult to compare to the tasks that Scoriels' group used (2012), and could suggest the MSCEIT may not be the best task to use since schizophrenia sufferers might have difficulties performing the MSCEIT due to executive function deficits, if the task is a measure of executive function rather than social cognition.

An important limitation is the multiplicity of tests and the consequent impracticability of correction of *p* values. This is further complicated by its being unclear how much scores on any particular test will vary with scores on another, making independence of scores uncertain. This makes cautious interpretation of the results a necessity, but the approach taken across the field is to make such exploratory analyses at this early stage of investigation of the drug's relative impact in different groups. In addition, the use of a single dose may have been insufficient in patients to allow the full effects of modafinil to accrue. Our previous study entailed 2 weeks' cognitive training while prescribed modafinil or placebo.

Do explanations in the literature for differences in the effects of modafinil on various samples based on lack of cognitive reserve or ceiling effects on tasks (Randall et al., 2005, Müller et al., 2013) apply here? The healthy volunteer sample was well matched on IQ and education, when compared to some previous samples. Despite this patients with limitations in executive function (or other aspects of cognition) may have been restricted in their ability to improve performance on other tasks following modafinil if executive function deficits impaired performance on other tasks that required executive processing to enable high level performance of core skills.

Comparing the two batteries, CANTAB proved more sensitive to changes in visual learning and processing that emerged only at trend levels of significance with MCCB. CANTAB was also able to identify changes in speed of planning that the MCCB, being paper-and-pencil based, cannot. At present the standard CANTAB schizophrenia battery lacks social and emotional processing measures that the MCCB includes, but the credentials of the MCCB as the pre-eminent tool for investigating neurocognitive performance are not unequivocally endorsed by these results.

Conclusions

Given the inconsistency of findings concerning modafinil in schizophrenia(Scoriels et al., 2012, 2013, Michalopoulou et al., 2015, Vreeker et al., 2015) the present study was mounted to test whether phase of illness was critical for the action of cognitive enhancers. We also compared cognitive assessment batteries' sensitivities. Here, modafinil significantly improved visual learning and processing as assessed by CANTAB, but not MCCB, in patients with early schizophrenia. It also led to slower performance during one CANTAB task . Effect sizes were often larger in the CANTAB and it had the capacity to detect effects on speed of performance, but the MCCB was able to detect changes in social cognition the CANTAB tasks used in this study could not. We conclude that whereas phase of illness may not be crucial to demonstrating the action of cognitive enhancers, the selection of assessment instrument may be. This has implications for clinical trial design in this important therapeutic area.

The complexity of modafinil's actions and the multiplicity of tests prevent firm conclusions. Tentatively, one can suppose that modafinil improved certain aspects of healthy volunteers' performance more than patients', but any such differences were too small to reach significance in most domains. Patients, unlike healthy volunteers, showed no significant benefit to visual processing or efficiency of strategic cognition, suggesting specific differences between the two groups. Otherwise, the fact that there are similar findings in each group across this and other studies is most easily explained by a fundamentally similar effect of modafinil in health and early illness across several areas of cognition. Larger studies or evidence from more direct investigation of the mechanisms of modafinil in health and schizophrenia, for instance by brain imaging, would be needed to establish this.

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Conflict of Interest

Prof Kapur has received grant support from AstraZeneca, Bristol-Myers Squibb and GlaxoSmthKline and has served as consultant, scientific advisor and had speaking engagements for AstraZeneca, Bioline, Bristol Meyers Squibb, Eli Lilly, Janssen (Johnson and Johnson), Lundbeck, NeuroSearch, Otsuka, Pfizer, Roche, Servier, Solvay and Wyeth.
Dr. Pandina is a full time employee of Janssen Research & Development and is a Johnson & Johnson stock-holder.
Prof Lewis has received consultancy fees from AbbVie, and Johnson and Johnson.
All other authors declare no competing interests.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Figure 1

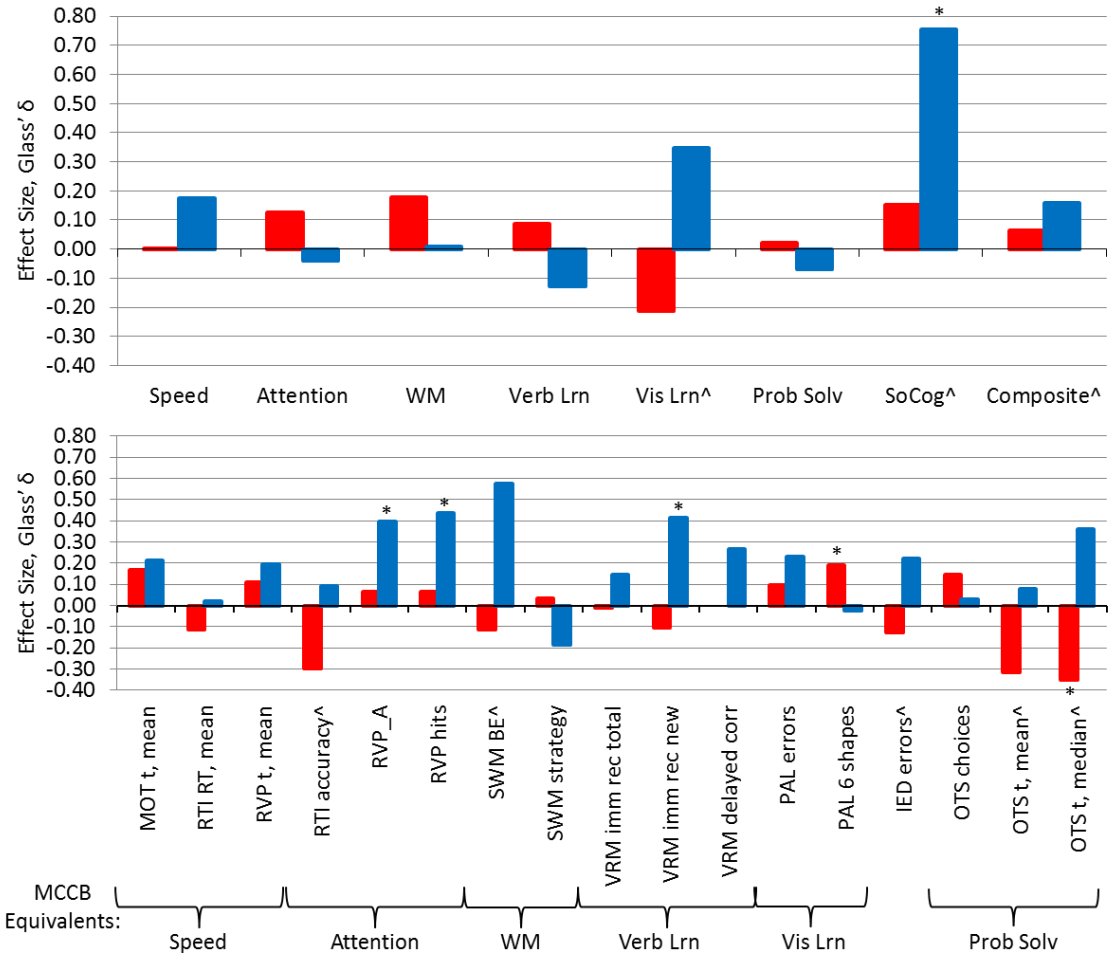
Effect Size, Glass' δ
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
-0.20
-0.30
-0.40
*
Speed
Attention
WM
Verb Lrn
Vis Lrn^
Prob Solv
SoCog^
Composite^
Effect Size, Glass' δ
MOT t, mean
RTI RT, mean
RVP t, mean
RTI accuracy^
RVP_A
RVP hits
SWM BE^
SWM strategy
VRM imm rec total
VRM imm rec new
VRM delayed corr
PAL errors
PAL 6 shapes
IED errors^
OTS choices
OTS t, mean^
OTS t, median^
MCCB Equivalents:
Speed
Attention
WM
Verb Lrn
Vis Lrn
Prob Solv

Table 1: Summary of participant characteristics and study variables

Variables	Healthy, n (%)	Recent-onset, n (%)
Site:	0	14 (35)
London	21 (100)	26 (65)
Manchester		
Ethnicity:		
White	16 (76)	22 (55)
Black/African	1 (5)	15 (37.5)
Other	4 (19)	3 (7.5)
Sex:		
Male	15 (71)	30 (75)
Female	6 (29)	10 (25)
Handedness:		
Right	20 (95)	34 (85)
Left	1 (5)	6 (15)
Smoker:		
Yes	14 (67)	23 (58)
No	7 (33)	17 (42)
	Healthy Mean (SD)	**Recent-onset Mean (SD)**
Age	25.81 (4.82)	25.63 (4.92)
Education, years full time	13.90 (2.74)	12.30 (3.77)
Chlorpromazine Equivalent	-	239.26 (119.37)
Duration of illness (months)	-	21.50 (9.36)
WTAR Standard Score	110.71 (14.61)	99.43 (13.99)
PANSS Positive	-	13.93 (4.06)
PANSS Negative	-	15.88 (5.61)
PANSS General	-	30.87 (6.27)
PANSS Total	-	60.70 (13.72)

WTAR – Wechsler Test of Adult Reading, PANSS – Positive And Negative Symptoms Scale

Table 2: Summary statistics and modafinil effects for MCCB and selected CANTAB tasks in volunteers with schizophrenia

	Modafinil		Placebo		Treatment effect	
MCCB Domain	**Mean**	**SD**	**Mean**	**SD**	**Mean Effect (95% CI)**	**P-value**
Speed of processing	40.55	14.19	40.21	15.19	0.34 (-2.27, 2.95)	0.801
Attention/Vigilance	36.74	10.94	35.32	10.56	1.43 (-0.63, 3.48)	0.174
Working memory	41.47	9.65	39.67	9.79	1.80 (-0.09, 3.69)	0.062
Verbal learning	41.04	11.36	40.28	10.45	0.75 (-2.70, 4.21)	0.670
Visual learning	39.75	12.54	42.29	12.12	-2.54 (-5.71, 0.64)	0.117
Reasoning & problem solving	44.30	11.13	43.65	10.77	0.65 (-1.70, 3.00)	0.590
Social cognition	40.19	11.52	38.76	9.41	1.43 (-0.85, 3.71)	0.220
MCCB Composite	34.73	13.79	33.73	13.53	0.99 (-1.21, 3.20)	0.378
CANTAB variable						
IED Errors Adjusted	32.25	29.17	28.09	21.52	4.16 (3.90, 12.23)	0.311
IED Stages completed	8.26	1.22	8.45	0.85	-0.20 (-0.56, 0.16)	0.284
MOT Mean Latency, s	808.62	152.11	843.41	175.31	-34.8 (-99.3, 28.7)	0.282
MOT Median error	764.98	139.33	800.39	153.78	-35.41 (-88.42, 17.60)	0.190
MOT Mean Error	7.29	2.26	7.71	2.17	-0.43 (-1.04, 0.18)	0.168
OTS Problems solved on first choice	9.80	2.54	9.35	2.89	0.46 (-0.24, 1.16)	0.202
OTS choices to correct	1.61	0.42	1.69	0.52	-0.08 (-0.18, 0.02)	0.105
OTS mean latency to correct, s	21127.5	9581.85	18471	6678.49	2656 (552, 4760)	0.013
OTS median latency to correct, s	17279.5	10078.33	13983	6275.19	3297 (758, 5835)	0.011
PAL total errors adjusted	16.12	17.44	19.00	22.98	-2.88 (-6.24, 0.48)	0.093
PAL errors 6 shapes adjusted	3.16	5.34	4.56	6.39	-1.40 (-2.54, -0.27)	0.015
RTI simple accuracy score	28.77	1.17	28.91	1.39	-0.14 (-0.61, 0.33)	0.553
RTI mean simple reaction time, s	327.39	82.36	318.78	65.32	8.60 (-6.88, 24.09)	0.276
RTI median simple reaction time, s	307.41	63.02	304.97	61.89	2.44 (-7.30, 12.18)	0.623
RTI SD simple reaction time, s	89.45	117.37	63.90	30.07	25.5 (-7.8, 58.8)	0.134

IED – Intra-Extra Dimensional Set Shift, MOT – Motor Screening, OTS – One Touch Stockings of Cambridge, PAL – Paired Associate Learning, RTI – Reaction Time

Table 3: Summary statistics and treatment effects for MCCB and CANTAB in healthy volunteers

	Modafinil		Placebo		Treatment Effects	
MCCB Domain	**Mean**	**SD**	**Mean**	**SD**	**Mean Effect (95% CI)**	**P-value**
Speed of processing	62.01	12.70	60.07	12.48	1.99 (-0.78, 4.75)	0.159
Attention/Vigilance	41.93	14.70	42.56	13.01	-0.63 (-5.12, 3.87)	0.785
Working memory	49.86	10.19	49.00	10.23	0.86 (-1.47, 3.19)	0.469
Verbal learning	42.91	9.33	44.46	10.93	-1.56 (-4.69, 1.58)	0.331
Visual learning	49.41	9.04	47.21	8.10	2.21 (-0.39, 4.80)	0.095
Reasoning and problem solving	53.24	8.35	53.97	8.66	-0.74 (-4.71, 3.24)	0.716
Social cognition	54.11	8.19	49.07	6.54	5.04 (2.23, 7.86)	<0.001
MCCB Composite	50.60	11.41	48.98	12.14	1.63 (-0.23, 3.48)	0.085
CANTAB variable						
IED Total Errors Adjusted	18.11	18.99	22.56	22.00	-4.44 (-7.74, -1.15)	0.008
IED Stages completed	8.86	0.48	8.63	0.87	0.24 (-0.04, 0.51)	0.095
MOT Mean Latency	696.62	170.99	743.53	199.98	-40.72 (-95.17, 13.74)	0.143
MOT Median error	663.88	154.19	704.60	195.03	-0.89 (-2.05, 0.28)	0.136
OTS solved on first choice	10.96	2.29	11.04	2.32	-0.08 (-0.81, 0.64)	0.822
OTS choices to correct	1.41	0.31	1.41	0.32	-0.00 (-0.08, 0.08)	0.965
OTS median latency to correct	10232.5	3614.45	10442.5	3011.38	-210 (-1533, 1114)	0.756
PAL total errors adjusted	7.6	7.30	9.96	13.18	-2.36 (-6.51, 1.79)	0.265
PAL total errors 6 shapes adjusted	1.29	2.06	1.32	1.85	-0.03 (-0.97, 0.92)	0.954
RTI simple accuracy score	28.74	1.50	29.17	0.87	-0.43 (-1.16, 0.30)	0.249
RTI median simple reaction time, s	279.76	33.37	286.67	38.31	-6.91 (-20.38, 6.56)	0.315
RTI 5 choice accuracy score	29.56	0.60	29.51	0.75	0.04 (-0.34, 0.42)	0.831
RTI 5 choice reaction time, s	314.00	56.94	308.70	39.92	5.30 (-9.64, 20.24)	0.487
RVP A’	0.95	0.04	0.92	0.05	0.02 (0.01, 0.03)	0.004
RVP Probability of hit	0.78	0.14	0.72	0.17	0.07 (0.03, 0.11)	0.001
RVP median latency	378.46	37.71	387.82	49.09	-9.36 (-24.70, 5.98)	0.232
SWM Strategy	13.25	4.15	13.86	4.09	-0.61 (-1.85, 0.63)	0.335
VRM: Free recall correct immediate	8.46	1.81	8.10	2.30	0.36 (-0.47, 1.19)	0.393
VRM: Free recall novel words immediate	0.09	0.30	0.37	0.58	-0.27 (-0.53, -0.03)	0.028
VRM: Recognition correct immediate	23.07	1.16	23.38	1.40	0.19 (-0.33, 0.72)	0.467
VRM: Recognition correct delayed	22.95	1.47	22.36	1.96	0.58 (-0.07, 1.24)	0.081

IED – Intra-Extra Dimensional Set Shift, MOT – Motor Screening, OTS – One Touch Stockings of Cambridge, PAL – Paired Associate Learning, RTI – Reaction Time, RVP – Rapid Visual Information Processing, SWM – Spatial Working Memory, VRM – Verbal Recognition Memory

Table 4: Comparison of modafinil effects between healthy volunteers and patients on MCCB

MCCB Domain	Interaction effect		
	Effect (SE)	P-value	95% CI
MCCB Composite	0.67 (1.69)	0.694	-2.65, 3.98
Speed of processing	1.62 (2.09)	0.437	-2.47, 5.72
Attention/Vigilance	-2.01 (2.18)	0.356	-6.27, 2.26
Working memory	-0.93 (1.57)	0.555	-4.01, 2.15
Verbal learning	-2.23 (2.69)	0.407	-7.50, 3.04
Visual learning	4.89 (2.46)	0.047	0.07, 9.71
Reasoning and problem solving	-1.45 (2.20)	0.510	-5.75, 2.86
Social cognition	3.57 (1.90)	0.060	-0.15, 7.30